Effect of metronidazole versus standard care on length of stay of patients admitted with severe infectious mononucleosis: a randomized controlled trial

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Abstract

Metronidazole may be of use in the treatment of infectious mononucleosis (IM). Our aim is to show that metronidazole shortens hospital stay for patients with severe IM. A single-centre randomized controlled trial was undertaken in patients admitted with severe IM, who were with a similar group treated by the standard care. Patients were blinded to which treatment arm they were in. Forty-two of these patients were enrolled in the trial. The primary endpoint was the difference in length of stay. This was significantly less in the metronidazole group (3.67 days v 4.67) (p 0.032). This study demonstrates that metronidazole has a role to play in severe infectious mononucleosis.

Keywords: Clinical trials, glandular fever, infectious mononucleosis, length of stay, metronidazole
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Metronidazole may be efficacious in the treatment of infectious mononucleosis (IM) [1]. A possible mechanism of its action in IM is through suppression of anaerobic flora [2–4]. Previous studies have demonstrated a rapid regression of symptoms in those taking metronidazole [1,5–8]; however, a single study showed no difference [9]. The hypothesis of our study is that metronidazole does shorten hospital stay.

The trial was a single-centre prospective randomized controlled trial. Patients were randomized to one of two arms, control or intervention, on a one-to-one basis. Patients diagnosed with IM were eligible if they were 15 or over and admitted to University Hospital Limerick (UHL), a tertiary referral centre. Three other hospitals in the region referred all cases for admission to UHL. Patients were recruited between 5 January 2010 and 11 April 2012. Patients were deemed appropriate for admission, and therefore severe [10], if they could not tolerate oral hydration or oral analgesia. Patients were excluded if they were allergic to penicillin, were pregnant, had an airway emergency, or were diagnosed with CMV mononucleosis or other mononucleosis-like infections. Steroids, if given in the Emergency Department (ED), were not continued once the patients were admitted.

The standard dose of metronidazole (500 mg TDS intravenously) was given at regular intervals at the same time as benzylpenicillin (1.2 g TDS). Benzylpenicillin is given to patients with IM to prevent a bacterial superinfection and complications such as Lemierre's syndrome [11,12]. It is part of the standard care, including supportive treatment with intravenous hydration, antipyretics and analgesics, which all patients received. No placebo was given.

The primary outcome measured was the difference in length of stay (LOS) in days. Patients were discharged when the consultant in charge of their care felt that they had made a sufficient recovery and were unlikely to represent to the hospital. Secondary outcomes included inflammatory markers, (white cell count, WCC) and high temperature (over 38°C).

Randomization was carried out by simple randomization, and allocation was concealed from the patient. The first author carried out enrollment, randomization and allocation concealment. Patients were blinded to which treatment arm they were in. Both groups received multiple injections and nurses were asked not to inform patients of which arm they were in.

Statistical analysis was undertaken using SPSS. Subgroup analysis was carried out on those who received steroids. CONSORT guidelines were followed [13].

Ethical permission was sought and granted by the Mid-Western Regional Ethics Research Committee (equivalent to IRB approval) and all patients signed an informed consent prior to being enrolled in the trial.

Fifty-one patients were admitted under the ENT service with infectious mononucleosis. Forty-two of these patients were enrolled in the trial. Eight patients were excluded: five were allergic to penicillin, two were under the age of 15, and one patient had an airway emergency. A single patient refused to partake in the trial. Patients were followed as in-patients and therefore there was no loss to follow-up. Three patients who were initially in the control group were started on

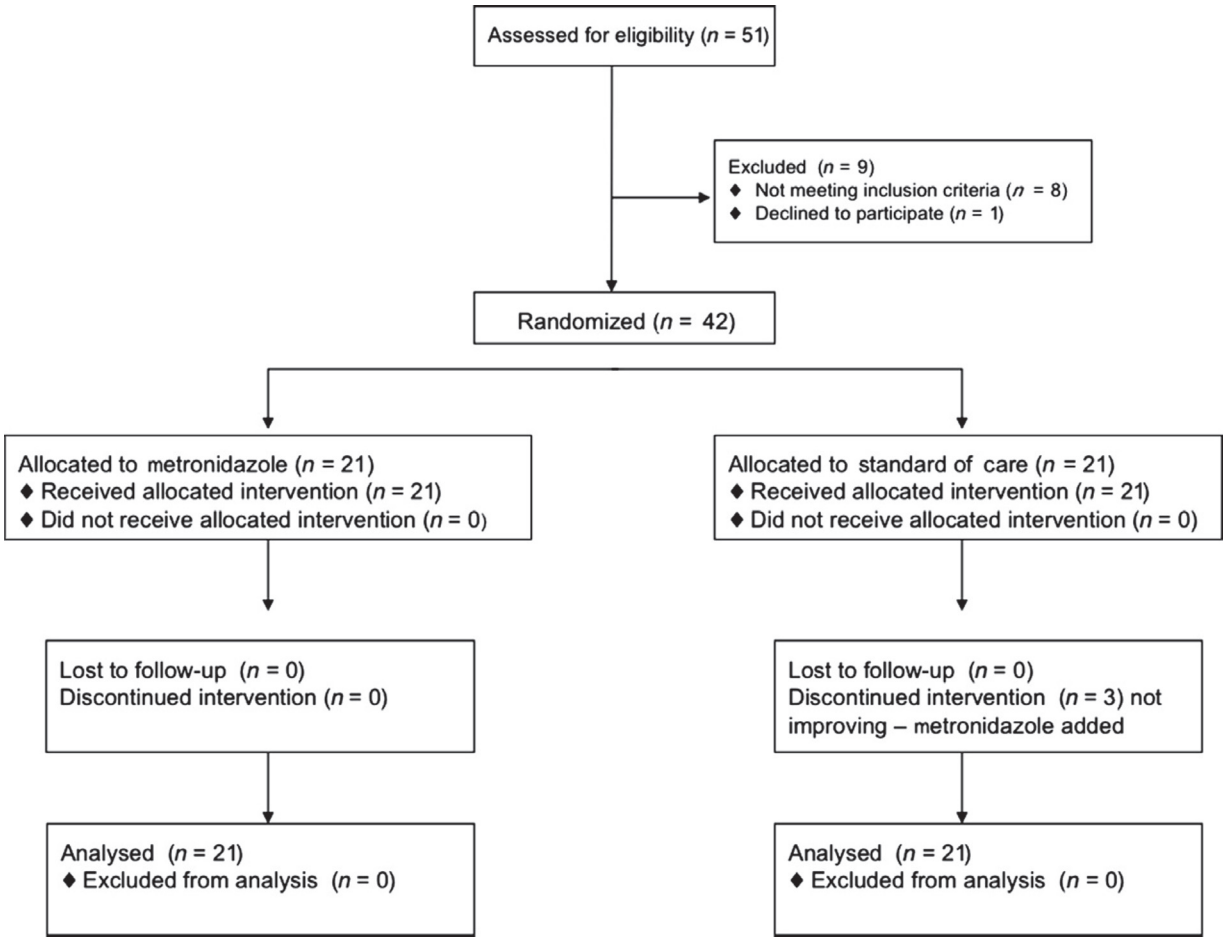

FIG. 1. Patient flow diagram.

metronidazole but failed to show any sign of improvement. These patients were analysed in their original group (Fig. 1). The trial was stopped when sufficient numbers were recruited to allow statistical analysis.

No significant difference in these baseline values, such as age, sex, symptomatic days prior to admission, primary care visits and antibiotic treatment prior to ED attendance, was found between the two groups.

The primary endpoint in the study was the difference in LOS. This was significantly less in the metronidazole group, with a mean of 3.67 compared to 4.67 in the standard care group (p 0.032). Differences in secondary endpoints were not significant (Table 1). No adverse effects from metronidazole were reported.

IM was once thought to be reminiscent of an anaerobic infection [1]. A number of studies were therefore undertaken to examine the possible role of metronidazole in the treatment of IM. The majority of these studies support the contention that metronidazole does indeed have a beneficial action in those with severe IM [1,6–8], with a single paper showing no significant effect [9]. The results of our study here concur with the majority of those previously undertaken that metronidazole shortens the duration of severe IM.

The limitations of this study include its small size. The trial is similar in size to the larger of the previously published studies on the same subject [7,9]. Due to their small size and the fact that the methods differ between them substantially, meta-analysis of these studies may be misleading [14]. The lack of publications with 'negative' results may be due to publication bias towards those with 'positive' results. From a recently published study on the epidemiology of the same population [15], a mean of 18.5 patients a year were admitted, therefore recruitment of 42 patients in 28 months was satisfactory.

Further weaknesses included the lack of a placebo. The trial was carried out within a clinical setting with no added funding. The primary author carried out most of the recruitment, allocation, randomization and data gathering, as well as the statistical analysis, thus leading to the risk of multiple biases, including reporting bias and multiplicity. Randomization was

TABLE 1. Results

	Metronidazole *n* = 21	Standard care *n* = 21	Difference (95%CI)	p-Value
Primary endpoints				
Length of stay in days, mean (SD)	3.67(1.35)	4.67(1.56)	1 (0.09 to 1.91)	0.032
Secondary endpoints				
Persistent high temperature (days)	0.76	1.00	0.238 (−0.08 to 1.32)	0.658
Decrease in WCC/day	1.98	2.10	0.12 (−0.87 to 1.1)	0.806
Ancillary analysis	**Steroids *n* = 12**	**No steroids *n* = 30**	**Difference (95%CI)**	**p-Value**
Length of stay in days, mean	4.25	4.13	0.12 (−1.2 to 0.95)	0.826
	Male *n* = 19	**Female *n* = 23**	**Difference (95%CI)**	**p-Value**
Length of stay in days, mean	4.21	4.13	0.80 (−0.89 to 1.1)	0.868
	Greater than 5 days	**5 days or less**	**Difference (95%CI)**	**p-Value**
Length of stay in days, mean	4.17	4.16	0.16 (−0.95 to 9.9)	0.974

also carried out by simple randomization, but baseline values in both groups are similar.

The results of this trial can be applied to a small but noteworthy cohort of patients: those with severe IM that require admission to hospital.

A greater number of anaerobes have been found on tonsils during an infection with IM than when the patient has recovered [4]. The Epstein–Barr virus exerts a transient suppression of immunoglobulin-coating of bacteria harboured on the tonsillar surfaces, with consequent abundant bacterial attachment to the epithelial cells and massive bacterial colonization on the palatine tonsils and penetration into the epithelial cells [16,17]. Metronidazole may help to hasten recovery by suppressing of the oral anaerobic flora that might contribute to the inflammatory process induced by the Epstein–Barr virus [2,18].

Our study has again demonstrated that metronidazole has a role to play in severe infectious mononucleosis. More trials on a larger scale and possibly in an outpatient setting are required.

Transparency Declaration

The authors declare no conflicts of interest.

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